# The Oxidation of *s*-Triazolo[4,3-*b*]pyridazines with Selenium Dioxide

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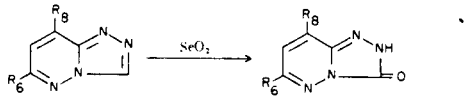
Received January 12, 1976

Some *s*-triazolo[4,3-*b*]pyridazines were oxidized to 2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-ones with selenium dioxide in nitrobenzene at 160-165° (external temperature) for 1-2 hours in 30-40% yields.

*J. Heterocyclic Chem.*, 13, 639 (1976).

The structural feature of *s*-triazolo[4,3-*b*]pyridazine is related to the purine ring system. Consequently, a large number of derivatives have been synthesized in anticipation of their pharmacological activities. Recently, some 3-oxo type compounds, 2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-ones, were synthesized by Lauria, *et al.*, from 3,6-dichloropyridazine and semicarbazide hydrochloride (1). We obtained some of these compounds by the oxidation of *s*-triazolo[4,3-*b*]pyridazines with selenium dioxide. The reactions were carried out in nitrobenzene at 160-165° (external temperature) for 1-2 hours in 30-40% yields.

Scheme I




Ia $R_6 = CH_3$, $R_8 = Cl$
IIa $R_6 = OCH_3$, $R_8 = H$
IIIa $R_6 = Cl$, $R_8 = H$
IVa $R_6 = R_8 = H$
Va $R_6 = Cl$, $R_8 = NHAc$

Ib $R_6 = CH_3$, $R_8 = Cl$
IIb $R_6 = OCH_3$, $R_8 = H$
IIIb $R_6 = Cl$, $R_8 = H$
IVb $R_6 = R_8 = H$
Vb(a) $R_6 = Cl$, $R_8 = NHAc$

(a) After hydrolysis, amine Vc was characterized.

In the oxidation of the compound IVa, two types of products were obtained. The major product was found to be compound IVb, but the structure of the minor product has not yet been ascertained and further study on this compound is in progress. In other instances, such a by-product was not obtained.

The structures of IIIb, IVb and Vc were established by the mixed melting point determination and ir spectral comparisons with authentic samples obtained by the Lauria's method (1). The structures of Ib and IIb were determined by elemental analyses, ir and nmr spectra.

Although the yields were not satisfactory probably due to the instability of this ring system, further experiments might be expected to improve them.

## EXPERIMENTAL

All melting points are uncorrected. Ir spectra were obtained in Nujol mulls with a Hitachi EPI-2 spectrometer. Nmr spectra were recorded on a JEOL JNM-PS-100 or a Hitachi R-20 spectrometer in DMSO-$d_6$ using TMS as an internal standard.

Materials.

6-Methyl-8-chloro-*s*-triazolo[4,3-*b*]pyridazine (Ia) (2), 6-methoxy-*s*-triazolo[4,3-*b*]pyridazine (IIa) (3), 6-chloro-*s*-triazolo-[4,3-*b*]pyridazine (IIIa) (3), *s*-triazolo[4,3-*b*]pyridazine (IVa) (4) and 6-chloro-8-acetylamino-*s*-triazolo-[4,3-*b*]pyridazine (Va) (5) were prepared as described in each reference.

6-Methyl-8-chloro-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-one (Ib).

A mixture of 3.4 g. (0.02 mole) of Ia and 3.3 g. (0.03 mole) of selenium dioxide in 50 ml. of nitrobenzene was heated at 160-165° (external temperature) for one hour. After cooling, the precipitate was collected by filtration, washed with ethanol and then with water. The residue was boiled with *ca.* 100 ml. of water (charcoal). The insoluble selenium was filtered, and the filtrate was concentrated and allowed to stand overnight to give 1.3 g. (35%) of Ib, m.p. 277-278° dec.; ir: 3150 (NH) and 1715 (CO) $cm^{-1}$; nmr: $\delta$ 2.39 (s, 3H, $CH_3$), 7.44 (s, 1H, $H_7$), 12.87 (br s, 1H, NH).

*Anal.* Calcd. for $C_6H_5ClN_4O$: C, 39.04; H, 2.73; N, 30.35. Found: C, 39.10; H, 2.51; N, 30.70.

6-Methoxy-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-one (IIb).

Compound IIa (2.3 g., 0.015 mole) was oxidized with 2.6 g. (0.023 mole) of selenium dioxide in 25 ml. of nitrobenzene at 160-165° (external temperature) for 2 hours. After cooling, the predipitate was collected and recrystallized from ethanol (charcoal) to give 0.9 g. (36%) of IIb, m.p. 268-270°; ir: 3170 (NH) and 1720 (CO) $cm^{-1}$; nmr: $\delta$ 3.94 (s, 3H, $CH_3$), 6.86 (d, J = 9.8 Hz, 1H, $H_7$), 7.75 (d, J = 9.8 Hz, 1H, $H_8$), 12.58 (br s, 1H, NH).

*Anal.* Calcd. for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.39; H, 3.55; N, 33.61.

6-Chloro-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-one (IIIb).

This compound was obtained in a similar manner as described for the oxidation of Ia, yield, 37%, m.p. 266-267° dec.; ir: 3150 (NH) and 1710 (CO) $cm^{-1}$. This sample was shown to be identical with the sample prepared by the method described in reference (1) by mixed melting point determination and comparison of the ir spectra.

2,3-Dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-one (IVb).

Compound IVa (1.8 g., 0.015 mole) was oxidized with 2.6 g. (0.023 mole) of selenium dioxide in 20 ml. of nitrobenzene at 160-165° (external temperature) for one hour. After cooling, the precipitate was collected, washed with a mixture of ethanol and benzene. The residue was boiled with *ca.* 100 ml. of ethanol. The insoluble by-product and selenium were filtered and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol/benzene (charcoal) to give 0.8 g. (39%) of IVb, m.p. 261-262.5°; ir: 3110 (NH) and 1695 (CO) $cm^{-1}$. This compound was shown to be identical with the sample prepared according to reference (1) by mixed melting point determination and comparison of the ir spectra.

6-Chloro-8-amino-2,3-dihydro-*s*-triazolo[4,3-*b*]pyridazin-3-one (Vc).

A mixture of 3.0 g. (0.014 mole) of Va and 3.0 g. (0.027 mole) of selenium dioxide in 50 ml. of nitrobenzene was heated at 160-165° (external temperature) for 2 hours. After cooling, the reaction mixture was added to *ca.* 50 ml. of water and allowed to stand overnight in a refrigerator. The precipitated material was collected, washed with ethanol and then with water. The residue was boiled with *ca.* 100 ml. of water (charcoal). After removal of selenium by filtration, 1 ml. of hydrochloric acid was added to the filtrate and refluxed for one hour. The substance which resulted was collected and recrystallized from acetic acid to give 0.3 g. (11%) of Vc, m.p. >300°. The ir spectrum of this compound was identical with those from the samples obtained by following methods.

Method A.

A mixture of 3.6 g. (0.022 mole) of 4-amino-3,6-dichloropyridzaine (6), 4.9 g. (0.044 mole) of semicarbazide hydrochloride and 50 ml. of 75% ethanol was refluxed with stirring in the presence of a few drops of hydrochloric acid for 20 hours. After cooling, the precipitate was collected and washed with water to give 1.5 g. (37%) of Vc, m.p. >300°; ir: 3350 ($NH_2$), 3280 ($NH_2$), 3170 (NH) and 1725 (CO) $cm^{-1}$; nmr: δ 5.95 (s, 1H, $H_7$), 7.53 (br s, 2H, $NH_2$), 12.69 (br s, 1H, NH). The analytical sample was purified by recrystallization from a large amount of acetic acid.

*Anal.* Calcd. for $C_5H_4ClN_5O$: C, 32.36; H, 2.17; N, 37.74. Found: C, 32.62; H, 2.11; N, 38.13.

Method B.

A mixture of 2.0 g. (0.013 mole) of 4-amino-6-chloro-3-hydrazinopyridazine (7), 1.7 g. (0.016 mole) of ethyl chloroformate and 0.9 g. (0.016 mole) of potassium hydroxide was refluxed in 50 ml. of ethanol for 2 hours. After removal of ethanol under reduced pressure, the residue was dissolved in 50 ml. of 10% aqueous potassium hydroxide, filtered and acidified with acetic acid. The precipitate was collected and washed with water to give 1.3 g. (54%) of Vc, m.p. >300°. The ir spectrum was identical with that from the sample prepared as described in method A.

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